Brief Report

The Additive Prognostic Value of Serial Plasma Interleukin-6 Levels over Changes in Brain Natriuretic Peptide in Patients with Acute Heart Failure

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ABSTRACT

Background: Elevated plasma interleukin-6 (IL-6) concentrations are frequently observed in patients with acute heart failure (AHF). However, the predictive value of serial IL-6 measurements beyond brain natriuretic peptide (BNP) remains poorly characterized.

Methods and Results: This was a retrospective analysis of the PROTECT cohort (2033 patients with AHF). Plasma IL-6 and BNP levels were determined on days 1, 2, 7 and 14 after admission for AHF in 1591 (78.3%), 1462 (71.9%), 1445 (71.1%) and 1451 (71.4%) patients, respectively. The primary endpoint was 180-day all-cause mortality. The median day-1 IL-6 concentration was 11.1 pg/mL (IQR: 6.6, 20.9) and decreased to 10.1 pg/mL (IQR: 5.6-18.5) at day-7. Higher cross-sectional IL-6 concentrations at all time-points predicted the primary endpoint, independent of a risk model for this cohort and changes in BNP. Each doubling of IL-6 between day-1 and day-7 predicted the primary endpoint independent of baseline IL-6 concentrations, the risk model, baseline BNP and changes in BNP [HR (95% CI): 1.18 (1.07-1.30), p=0.0013]. Collectively, 214 (17%) patients experienced at least a doubling of their IL-6 concentrations between day-1 and day-7.

Conclusions: We demonstrate that the temporal evolution patterns of IL-6 in patients with AHF have additive prognostic value independent of changes in BNP. (*J Cardiac Fail 2021;27:808−811*)

Keywords: Serial, change, IL-6, BNP, NT-proBNP, landmark.

Introduction

Elevated plasma concentrations of interleukin-6 (IL-6) are frequently observed in patients with acute and chronic heart failure (AHF/CHF) and are associated with worse clinical outcomes.[1] Previous relatively small cohort studies (n<75) have demonstrated that serial IL-6 measurements can predict adverse outcomes in HF.[2−4] However, the prevalence and predictors of elevated serial IL-6 measurements and their relationship with prognosis in patients with AHF remain poorly characterized. Additionally, it is unknown whether the prognostic value of changes in serial IL-6 is independent of brain natriuretic peptide (BNP). Therefore, we investigated the added prognostic value of serial IL-6 measurements in a large, well-characterized cohort of patients with AHF.

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Patients and Methods

The design and results of the PROTECT trial have been described previously. [5] Briefly, PROTECT was a multicenter randomized, double-blind, placebo-controlled trial studying rolofylline for the treatment of AHF regardless of left ventricular ejection fraction (LVEF), with overall neutral results. Major inclusion criteria for the study cohort, consisting of 2033 patients, were dyspnea at rest/minimal activity, impaired renal function, a BNP level ≥500 pg/mL or an N-terminal pro-BNP level ≥2000 pg/mL, intravenous loop-diuretic therapy, and enrollment within 24 hours after admission. The primary endpoint of this retrospective analysis was all-cause mortality at 180 days, a secondary endpoint of the original PROTECT trial. Outcomes were independently adjudicated. Serial plasma IL-6 and BNP levels were determined using high-sensitivity single molecule counting technology (Singulex Inc.) on days 1, 2, 7 and 14 after admission in 1591 (78.3%), 1462 (71.9%), 1445 (71.1%) and 1451 (71.4%) patients, respectively. Changes in IL-6 between baseline (day 1) and day 7 after admission could be determined in 1256 patients (61.8%). All biomarkers were transformed to a log2-scale to denote a doubling of the original values per 1-unit change.

Cox regression analysis was used to investigate the effect of baseline IL-6 concentrations on 180-day all-cause mortality (n=278/1591) and to adjust for confounding using a previously published prognostic model for this cohort[5] and baseline BNP. Landmark analyses[6] at days 2, 7 and 14 were used to investigate time-dependent effects of IL-6 on prognosis using the cross-sectional IL-6 measurements at the corresponding timepoints. A separate landmark analysis was performed using the log2-fold change in IL-6 levels between baseline and day 7. Each landmark analysis was also corrected stepwise for the same risk model and for changes in BNP concentrations between the landmark and the immediately preceding timepoint, as well as BNP and IL-6 concentrations of the immediately preceding timepoint. Statistical analyses were carried out using R-Studio v.3.6.0.

Results

Patients without available baseline IL-6 measurements (n=442) were younger and more often male. The median age of the study participants was 73 years (interquartile range [IQR]: 63, 79) and 541 (34%) were women. Median LVEF was 30% (IQR: 22-40), 100 (13%) patients had an LVEF≥50% and the median BNP concentration in the entire group was 449 pg/mL (IQR: 255, 801). The median baseline IL-6 concentration was 11.1 pg/mL (IQR: 6.6, 20.9). Between baseline and day 7, concentrations of IL-6 decreased on average to a median of 10.1 pg/mL (IQR: 5.6-18.5). Median log2-fold change between the two timepoints was -0.13 (IQR: -0.86, 0.66). Patients with higher baseline IL-6 levels were older [1st vs. 2nd vs. 3rd tertile median age (IQR): 71 (61, 78) vs. 72 (64, 79) vs. 75 (66-80) years, p<0.001], had lower estimated glomerular filtration rates [49 (38, 65) vs. 45 (33, 59) vs. 43 (32, 55) mL/min/1.73 m^2, p<0.001], and higher BNP levels [326 (206, 594) vs. 475 (276, 840) vs. 551 (300, 957) pg/mL, p<0.001]. Sex and LVEF≥50% were not associated with differences in IL-6 concentrations (p= 0.88 and 0.93 respectively).

At all examined time-points, higher cross-sectional concentrations of IL-6 were associated with a higher risk of 180-day all-cause mortality, independent of the previously published risk model. Further correction for changes in BNP did not attenuate the association between IL-6 and higher 180-day all-cause mortality (Table 1). Serial IL-6 measurements also demonstrated incrementally stronger associations with adverse outcomes proportional to the time of the measurement since admission (Table 1). In a separate analysis, each doubling of IL-6 concentrations between baseline and day 7 conferred a significantly higher risk of all-cause mortality when corrected for baseline IL-6 concentrations [hazard ratio (95% confidence interval): 1.26 (1.15-1.39), p<0.0001] and remained significant when corrected for the existing risk model [1.24 (1.12-1.37), p<0.0001], as well as for baseline BNP and changes in BNP [1.18 (1.07-1.30), p=0.0013] (Figure 1). In total, 214/1256 patients (17%) included in this analysis experienced at

Table 1. Cox regression and landmark analyses for predicting the primary endpoint of all-cause mortality at 180 days. For each of the corresponding endpoint, the measured IL-6 levels were used as predictors for the combined outcome and corrected for confounding factors in a stepwise manner. Hazard ratios are presented for each log2-fold change (doubling) of IL-6 levels. *p≤0.05.

Model	Day 1		Day 2		Day 7		Day 14	
	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value	HR (95% CI)	p-value
A.	1.38 (1.29-1.48)	<**0.0001***	1.32 (1.18-1.47)	<**0.0001***	1.44 (1.30-1.60)	<**0.0001***	1.65 (1.46-1.85)	<**0.0001***
B.	1.27 (1.17-1.37)	<**0.0001***	1.28 (1.14-1.43)	<**0.0001***	1.38 (1.23-1.55)	<**0.0001***	1.54 (1.36-1.74)	<**0.0001***
C.	1.25 (1.15-1.36)	<**0.0001***	1.27 (1.12-1.43)	<**0.0001***	1.29 (1.14-1.45)	<**0.0001***	1.56 (1.37-1.77)	<**0.0001***

A: Model including analysis of cross-sectional IL-6 measurements at the corresponding designated timepoint (corrected for IL-6 measured at the immediately preceding timepoint after day 1).

B: Included model A and further corrected for the previously published risk prediction model for this cohort[5]. This included age, previous heart failure hospitalization, the presence of oedema, systolic blood pressure, serum creatinine, sodium, blood urea nitrogen and albumin.

C: Included model B and further corrected for day 1 BNP for the analysis of day 1 IL-6 and for log2-fold change in BNP, between consecutive measurements for each corresponding timepoint (i.e. deltaBNP 1-2, 2-7 and 7-14) and the BNP measurements of the immediately preceding measurement timepoint.

IL-6 interleukin-6; BNP brain-type natriuretic peptide; HR hazard ratio; 95% CI 95% confidence interval

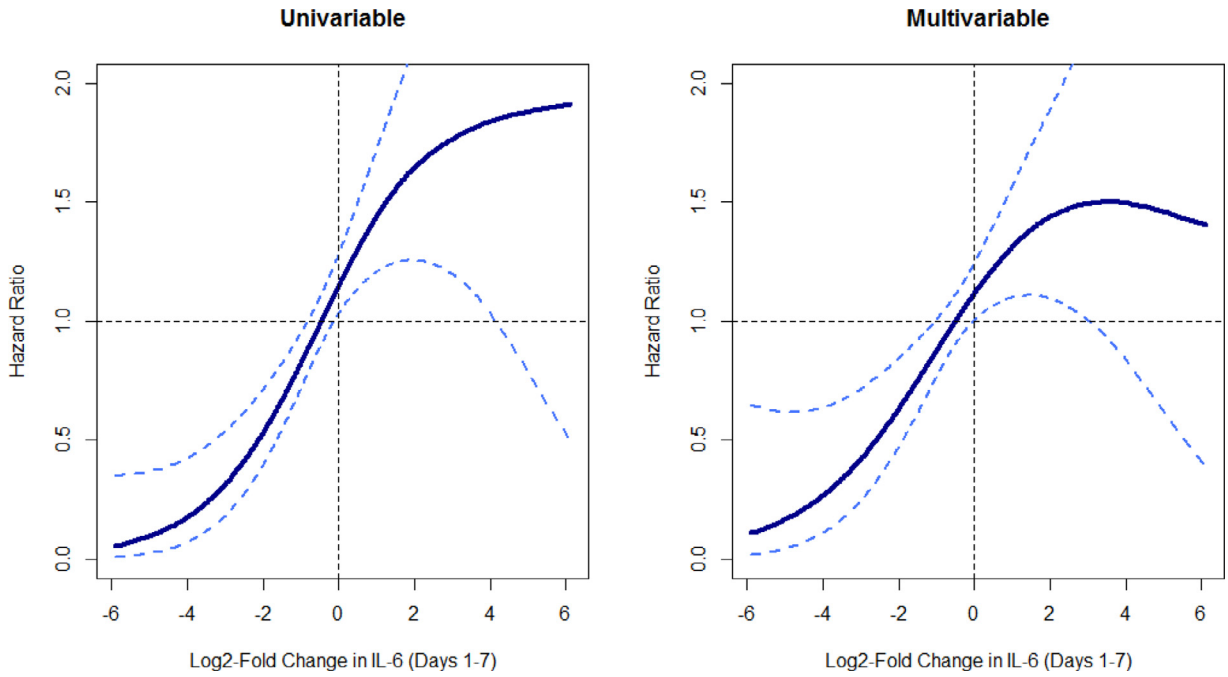

Figure 1. Natural penalized splines with 95% confidence intervals of the hazard ratios for all-cause mortality at 180 days as a function of Log2-Fold changes in IL-6 plasma concentrations between baseline (day 1) and day 7 after admission. The left-sided figure is only corrected for IL-6 at day 1. The right-sided figure is corrected for the same but also includes the previously published predictive model for this cohort[5], BNP at day 1 and change in BNP between days 1 and 7. IL-6 interleukin-6; BNP brain natriuretic peptide.

least a doubling of their IL-6 concentrations between baseline and day 7.

Discussion

To our knowledge, this is the first study to demonstrate that the temporal evolution patterns of IL-6 plasma concentrations are associated with prognosis in patients with AHF, independent of known confounders or changes in BNP levels. This complements previous studies that demonstrated associations of serial IL-6 measurements with prognosis. The largest of these studies evaluated 73 patients with AHF and reported IL-6 plasma levels at 12, 24, 48 and 72 hours and 1, 2 and 4 weeks after admission[3]. The authors concluded that changes in IL-6 correlated with changes in pulmonary capillary wedge pressure and that IL-6 was significantly higher in patients with AHF that required mechanical ventilation compared with those that did not. Furthermore, IL-6 levels together with pulmonary pressures decreased with time in stark contrast to interleukin-1β and tumor necrosis factor-α which remained elevated throughout the study. These findings suggest that IL-6 may better reflect short-term clinical improvement.

Another study also evaluated the relationship between 11 healthy controls and 19 patients with AHF with regard to their circulating monocyte subsets (classic, intermediate, non-classic) next to plasma IL-6 measurements at admission and discharge, and reported that IL-6 levels and monocyte profiles resemble those of healthy controls more closely following standard-of-care treatment.[7] IL-6 is the primary cytokine that mediates the transition from acute to chronic inflammation by promoting a shift from a neutrophilic to a mononuclear cell infiltrate.[8] Mononuclear cells are the main immune cells responsible for producing IL-6[8] and the principal mediators of the so-called cardiosplenic axis, a process in which heart-spleen cross-talk mediates cardiotoxic immune responses.[9] The cardiosplenic axis has in turn been shown to have an important causative role in HF in numerous animal studies. Namely, it has been demonstrated that splenectomy in mice with ischaemic HF leads to reverse LV remodeling, reduced LV size, improved LVEF and a reduced number of macrophages in the heart, while adoptive transfer of mononuclear splenocytes from mice with HF to healthy mice produces a HF phenotype with LV dilatation, reduced LVEF, interstitial cardiac fibrosis and increased lung weights.[9] Similarly, in humans after an acute coronary syndrome, spleen metabolic activity measured with positron emission tomography was increased and was associated with pro-inflammatory changes in leukocytes, elevated C-reactive protein and increased arterial wall inflammation.[10] A study of cardiac, splenic and bone marrow autopsy findings in patients that died at different timepoints after having an acute myocardial infarction demonstrated a clear monocyte depletion chiefly from the spleen and secondarily from the bone marrow, which coincided with monocytic infiltration of the heart.[11] Lastly, there is also evidence that splenic metabolic activity inversely correlates with diastolic function in both mice and humans with HF with preserved ejection fraction, thus also suggesting that the actions of the cardiosplenic axis are not limited to HF with reduced ejection fraction. Collectively, our findings of the prognostic capacity of serial IL-6 plasma concentrations in patients with AHF may potentially indicate that those with persistently

elevated levels at each time-point or those with increases between two time-points show persistent inflammation and activation of the cardiosplenic axis. This is in line with the finding that cross-sectional IL-6 levels exerted a stronger effect on prognosis proportional to the time from study inclusion. (strongest effect at 14 days), which also is in agreement with the role of IL-6 in mediating the transition from acute to chronic inflammation. IL-6 may thus serve as a potential therapeutic target in these patients.

Interestingly, changes in BNP did not influence the predictive capacity of serial IL-6 in our study, and the association of IL-6 with prognosis increased in strength with follow-up time. Myocardial stretch is known to induce both the production of BNP and IL-6[12] , and BNP closely reflects hemodynamic demands on the heart and decongestion. However, the resolution of mechanical stress might not be sufficient to halt IL-6 production, as might be the case with the persistent activation of the cardiosplenic axis as stated previously.[11] Collectively, our findings suggest that IL-6 is an important prognostic marker in HF, and support further investigation into potential therapeutic applications involving the modulation IL-6 activity for the treatment of HF.

Conclusions

To conclude, this study demonstrates that the temporal evolution patterns of IL-6 have additive prognostic value independent of changes in BNP in patients with AHF, and provides a rationale for further investigation of the magnitude and trajectories of these patterns as adjuncts to potential clinical applications in AHF.

Declaration of Competing Interest

The PROTECT trial was supported by NovaCardia, a subsidiary of Merck & Co. Dr. Cleland was on the Steering Committee (and received payment) for the PROTECT trial; served on the advisory board (and received payment) for MSD. Dr. O'Connor is a consultant to Merck & Co., Inc. Dr. Ponikowski has received honoraria from Merck & Co., Inc. Drs. Davison and Cotter are employees of Momentum Research Inc., which was contracted to perform work on the project by Merck & Co., Inc. Dr. Metra has received honoraria and reimbursements from NovaCardia (sponsor of the study) and Merck & Co., Inc. Dr. Givertz has received institutional research support and served on a scientific advisory board for Merck & Co., Inc. Dr. Teerlink has received research funds and consulting fees from Merck & Co., Inc. Dr. Mentz has received research support and honoraria from Merck & Co, Inc and has served on an advisory board for Roche. Dr. Voors has received speaker and consultancy fees from Merck & Co., Inc.; was on the Steering Committee for the PROTECT trial; and received research support from Alere, Amgen, Bayer, Boehringer Ingelheim, Cardio3Biosciences, Celladon, GSK, Novartis, Roche Diagnostics, Servier, Singulex, Sphingotec, Stealth Peptides, Trevana, Vifor Pharma, and ZS Pharma. JT received consultancy fees from Roche diagnostics and personal fees from Olink proteomics. Dr. van der Meer received consultancy fees and/or grants from Novartis, Corvidia, Singulex, Servier, Vifor Pharma, Astra Zeneca, Pfizer and Ionis. All other authors have no relationships to disclose that could be construed as a conflict of interest with regard to this manuscript.

References

1. Markousis-Mavrogenis G, Tromp J, Ouwerkerk W, Devalaraja M, Anker SD, Cleland JG. The clinical significance of interleukin-6 in heart failure: results from the BIOSTAT-CHF study. Eur J Heart Fail 2019;21:965–73.
2. Sato Y, Takatsu Y, Kataoka K, Yamada T, Taniguchi R, Sasayama S. Serial circulating concentrations of C-reactive protein, interleukin (IL)-4, and IL-6 in patients with acute left heart decompensation. Clin Cardiol 1999;22:811–3.
3. Suzuki H, Sato R, Sato T, Shoji M, Iso Y, Kondo T. Time-course of changes in the levels of interleukin 6 in acutely decompensated heart failure. Int J Cardiol 2005;100:415–20.
4. Goonewardena SN, Stein AB, Tsuchida RE, Rattan R, Shah D, Hummel SL. Monocyte subsets and inflammatory cytokines in acute decompensated heart failure. J Card Fail 2016;22:358–65.
5. Cleland JG, Chiswell K, Teerlink JR, Stevens S, Fiuzat M, Givertz MM. Predictors of postdischarge outcomes from information acquired shortly after admission for acute heart failure: a report from the placebo-controlled randomized study of the selective a1 adenosine receptor antagonist rolofylline for patients hospitalized with Acute Decompensated Heart Failure and Volume Overload to Assess Treatment Effect on Congestion and Renal Function (PROTECT) Study. Circ Hear Fail 2014;7:76–87.
6. Morgan CJ. Landmark analysis: a primer. J Nucl Cardiol 2019;26:391–3.
7. Goonewardena SN, Stein AB, Tsuchida RE, Rattan R, Shah D, Hummel SL. Monocyte subsets and inflammatory cytokines in acute decompensated heart failure. J Card Fail 2016;22:358–65.
8. Gabay C. Interleukin-6 and chronic inflammation. Arthritis Res Ther 2006;8:S3.
9. Prabhu SD. The cardiosplenic axis is essential for the pathogenesis of ischemic heart failure. Trans Am Clin Climatol Assoc 2018;129:202–14.
10. Emami H, Singh P, Macnabb M, Vucic E, Lavender Z, Rudd JHF. Splenic metabolic activity predicts risk of future cardiovascular events: demonstration of a cardiosplenic axis in humans. JACC Cardiovasc Imaging 2015;8:121–30.
11. Van Der Laan AM, Ter Horst EN, Delewi R, Begieneman MPV, Krijnen PAJ, Hirsch A, et al. Monocyte subset accumulation in the human heart following acute myocardial infarction and the role of the spleen as monocyte reservoir. Eur Heart J Eur Heart J 2014;35:376–85.
12. Nian M, Lee P, Khaper N, Liu P. Inflammatory cytokines and postmyocardial infarction remodeling. Circ Res 2004;94:1543–53.